

Concomitant Use of *Treximet* and *Imitrex* Injection

This information is provided in response to your request for information about *Treximet*® (sumatriptan and naproxen sodium) Tablets. *Treximet* is a single-tablet formulation of sumatriptan 85 mg, formulated with RT Technology, and naproxen sodium 500 mg.

This information is provided in response to your request for information about *Imitrex*® (sumatriptan succinate) Injection.

SUMMARY

- In an open-label, randomized, crossover study, sumatriptan exposure (AUC_{0-14} and C_{max2}) following *Treximet* plus *Imitrex* injection 4 mg 2 hours later did not exceed the exposure following an *Imitrex* 100 mg tablet plus *Imitrex* 100 mg tablet administered 2 hours later.
- Sumatriptan exposure (AUC_{0-14}) following *Treximet* plus *Imitrex* injection 6 mg 2 hours later did not exceed the exposure following an *Imitrex* 100 mg tablet plus *Imitrex* 100 mg tablet administered 2 hours later; however, sumatriptan C_{max2} was higher.
- Adverse events were generally similar in type and frequency between the treatments, but overall frequency was slightly lower for *Treximet* plus *Imitrex* injection 4 mg 2 hours later, the treatment giving lowest exposure to sumatriptan.
- Important safety information is found in the attached Prescribing Information.
- The prescribing information for this product contains a boxed warning. Please consult the WARNING section of the attached prescribing information for further details and for important safety information.

STUDY DESIGN

An open-label, randomized, three-period, crossover study in healthy male and female volunteers between the ages of 18 and 55 evaluated pharmacokinetic parameters of the concomitant use of *Treximet* and *Imitrex* injection delivered with Imitrex STATdose System™.⁽¹⁾ Subjects were randomly assigned to one of six treatment sequences – ABC, ACB, BAC, BCA, CAB, and CBA (see Table 1). Dosing sessions were separated by a minimum of 7 days. Regimen C, *Imitrex* 100 mg tablet followed 2 hours later by a second *Imitrex* 100 mg tablet, is an established dose regimen for *Imitrex* and was therefore selected as the reference regimen.

Table 1. Dosing Regimens

Regimen	Description
A	<i>Treximet</i> followed 2 hours later by <i>Imitrex</i> injection 4 mg
B	<i>Treximet</i> tablet followed 2 hours later by <i>Imitrex</i> injection 6 mg
C	<i>Imitrex</i> 100 mg tablet followed 2 hours later by a second <i>Imitrex</i> 100 mg tablet

The primary objectives were to:

- demonstrate that sumatriptan exposure (as measured by C_{max} after second dose [C_{max2}] and AUC_{0-14}) following *Treximet* plus *Imitrex* injection 4 mg administered 2 hours later (Regimen A) does not exceed the exposure that occurs following the reference Regimen C,
- demonstrate that sumatriptan exposure (as measured by C_{max} after second dose [C_{max2}] and AUC_{0-14}) following *Treximet* plus *Imitrex* injection 6 mg administered 2 hours later (Regimen B) does not exceed the exposure following the reference Regimen C.

Additional endpoints evaluated include the safety and tolerability of *Treximet* across the three regimens as well as comparison of blood pressures in Regimens A and B versus C.

A mixed effects linear analysis of variance (ANOVA) model was fitted to log transformed primary pharmacokinetic parameters (AUC_{0-14} and C_{max2}) separately to assess the regimens (A versus C and B versus C). Continuous cardiovascular monitoring was performed beginning 1 hour prior to dosing administration and continuing through 10 hours post-first dose for all dosing sessions.

PHARMACOKINETIC RESULTS

Individual plasma sumatriptan AUC_{0-14} and C_{max2} are presented in Table 2 below.

Table 2. Summary of Sumatriptan Pharmacokinetic Parameters AUC_{0-14} and C_{max2}

Parameter	Treatment	n	Geometric Mean (95% CI)
AUC_{0-14} (ng.h/mL)	A	26	210 (192,230)
	B	26	249 (229,272)
	C	26	348 (307,395)
C_{max2} (ng/mL)	A	27	72.0 (64.6,80.3)
	B	26	90.6 (79.4,103)
	C	26	73.2 (63.4,84.5)

n=number of subjects with non-missing values

A summary of the statistical analysis of plasma sumatriptan pharmacokinetic parameters C_{max2} and AUC_{0-14} are shown in Table 3 below.

Table 3. Statistical Analyses of Sumatriptan Pharmacokinetic Parameters

Parameter	Comparison	Test	Reference	LS Means Ratio	90% CI (Lower, Upper)
C_{max2} (ng/ml)	A-C	72.08	72.32	1.00	(0.88, 1.13)
AUC_{0-14} (ng.h/ml)	A-C	212.13	345.36	0.61	(0.57, 0.66)
C_{max2} (ng/ml)	B-C	90.90	72.32	1.26	(1.11, 1.43)
AUC_{0-14} (ng.h/ml)	B-C	247.71	345.36	0.72	(0.67, 0.77)

Note: LS Means Ratio is the ratio of test over reference

Regimen A versus Regimen C

Sumatriptan exposure (AUC_{0-14} and C_{max2}) following *Treximet* plus *Imitrex* injection 4 mg 2 hours later did not exceed the exposure following an *Imitrex* 100 mg tablet plus an *Imitrex* 100 mg tablet administered 2 hours later.

Regimen B versus Regimen C

Sumatriptan exposure (AUC_{0-14}) following *Treximet* plus *Imitrex* injection 6 mg 2 h later did not exceed the exposure (AUC_{0-14}) following the *Imitrex* 100 mg tablet plus an *Imitrex* 100 mg tablet administered 2 hours later. However, sumatriptan C_{max} after the second dose (C_{max2}) was on average 1.26 fold higher following administration of *Treximet* plus *Imitrex* injection 6 mg 2 hours later compared to *Imitrex* 100 mg tablet plus an *Imitrex* 100 mg tablet administered 2 hours later.

Comparison with Data from SUM20040

A previous study (SUM20040) assessed the safety, tolerability and pharmacokinetics of a 3 mg subcutaneous dose of sumatriptan administered 2 hours after a single *Imitrex* 100 mg tablet relative to two *Imitrex* 6 mg injections administered one hour apart in healthy subjects.⁽²⁾ In this study, the regimen of two 6 mg injections administered one hour apart was the reference. It can be seen from the pharmacokinetic parameters for the reference regimen described in Table 4 below that the C_{max} following administration of Regimen B in TRX103629 (*Treximet* plus *Imitrex* injection 6 mg administered 2 hours later) of 90.6

(79.4,103) ng/mL does not exceed the C_{max} of two *Imitrex* 6 mg injections administered one hour apart 109 (99.8 - 118) ng/mL.

Table 4. Pharmacokinetic Parameters for Two Doses of *Imitrex* Injection 6 mg Administered 1 Hour Apart

Parameter	C_{max}^* (ng/mL)	$t_{max}^{*\dagger}$ (hours)	AUC_{0-2}^* (ng.h/mL)	AUC_{0-t}^{\ddagger} (ng.h/mL)	$AUC_{0-\infty}^{\ddagger}$ (ng.h/mL)
<i>Imitrex</i> injection 6 mg plus <i>Imitrex</i> injection 6 mg administered one hour later (n = 34)	109 (99.8 - 118)	1.3 (1.1 – 1.3)	101 (94.6 - 107)	207 (195 - 219)	208 (196 - 221)
*Following the second dose					
\dagger Median (range) time relative to first dose					
\ddagger Pooled exposure across first and second doses					

SAFETY RESULTS

There were no deaths, non-fatal serious adverse events or pregnancies in this study. All adverse events were of mild severity and resolved by the end of the study. There was one withdrawal for an adverse event of folliculitis which was considered by the investigator to be unrelated to study medication. Adverse events were generally similar in type and frequency between the treatments but overall frequency was slightly lower for treatment A, the treatment giving lowest exposure to sumatriptan.

Table 5. Most Frequent ($\geq 2\%$) Adverse Events

	Treatment A (n=27)	Treatment B (n=26)	Treatment C (n=27)
Headache	3 (11%)	3 (12%)	4 (15%)
Dizziness	2 (7%)	1 (4%)	2 (7%)
Paraesthesia	1 (4%)	2 (8%)	1 (4%)
Nausea	0	5 (19%)	4 (15%)
Dyspepsia	0	2 (8%)	2 (7%)
Vessel puncture site pain	0	3 (12%)	2 (7%)
Nasal discomfort	1 (4%)	2 (8%)	1 (4%)
Hyperhidrosis	0	2 (8%)	0

Systolic and diastolic blood pressures were on average slightly lower for regimens A and B compared to C for all the comparisons of weighted means. No major violations of modelling assumptions were found.

Some information contained in this response may not be included in the approved Prescribing Information. This response is not intended to offer recommendations for administering this product in a manner inconsistent with its approved labeling.

In order for GlaxoSmithKline to monitor the safety of our products, we encourage healthcare professionals to report adverse events or suspected overdoses to the company at 888-825-5249. Please consult the attached Prescribing Information.

This response was developed according to the principles of evidence-based medicine and, therefore, references may not be all-inclusive.

REFERENCE(S)

1. Data on File. DOF_TRX103629. *
2. Data on File. DOF_SUM20040. *